

EDITORIAL COMMENT

Detection of Vulnerable Coronary Artery Plaques

Lesion Level Risk Assessment Within the Coronary Arterial Tree?*

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Progressive atherosclerotic disease and its clinical sequelae remain the number one cause of mortality in the U.S. The majority of patients with acute coronary syndromes (ACS) present with unstable angina, acute myocardial infarction, or sudden cardiac death secondary to sudden luminal thrombosis. Until recently, the prevailing clinical perception of atherosclerosis was that of advancing luminal stenosis with less attention paid to the condition of the vessel wall. Although the demonstration of luminal obstruction or consequent reduction in blood flow may explain symptoms of coronary disease and abnormalities on perfusion imaging, it does not accurately reveal the patient's future likelihood of experiencing an acute coronary event. Angiographic

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and intravascular ultrasound (IVUS) studies of coronary arteries before and after ACS have found that hemodynamically insignificant lesions typically cause these events (1–5). This has led to the misperception that thromboses occur at sites of minimal atherosclerotic disease, primarily based on the lack of angiographic luminal obstruction. Pathological studies and more recent IVUS and optical coherence tomography data demonstrate significant plaque accumulation at these lesion sites vulnerable to rupture that can be masked by expansive vessel remodeling (6–10).

Within any given patient, different types of potential vulnerable plaques (VPs) with various underlying histopathology and biology exist. Coronary luminal thrombosis occurs from 3 different

pathologies (plaque rupture, plaque erosion, and calcified nodules), with plaque rupture being the most common (11). The pre-thrombosed lesion that most resembles acute plaque rupture is the thin cap fibroatheroma (TCFA), characterized by a necrotic core with a thin (<65 μm) fibrous cap, containing rare smooth muscle cells but numerous macrophages. Autopsy studies have demonstrated a strong correlation between plaque morphology and ACS pathology, with TCFA typically present at sites <50% diameter stenosis. Identification with subsequent therapeutic targeting of these TCFA in living patients may help reduce the incidence of ACS and sudden cardiac death. To evaluate plaque vulnerability, lesion level assessment with a variety of techniques (noninvasive and invasive imaging modalities) is being rigorously pursued. One such technique is near-infrared spectroscopy (NIRS).

Near-infrared spectroscopy, a technique routinely used in the physical sciences to determine chemical composition of substances, is under active investigation as a potential tool to identify VP (12–14). The impetus for this work is the high likelihood that plaques with a distinct chemical composition (i.e., inflamed TCFA) represent VPs that may be prone to rupture and result in ACS. The goal of intracoronary NIR spectroscopy is to provide a “chemogram” of the coronary artery wall to serve as an index of vulnerability. In this issue of *JACC* (*JACC: Cardiovascular Imaging*), Gardner et al. (15) assessed the diagnostic accuracy of NIRS compared with that of histology in coronary artery autopsy specimens.

Scanning NIRS was performed on 212 coronary artery segments from 84 autopsy hearts, with the goal of demonstrating the ability of the NIRS system to detect lipid core plaques compared with that of the gold standard of histology. A unique custom fixture was used to mount the coronary

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segments (allowing fluid flow and catheter entry) then examined with the NIRS in a pullback manner similar to IVUS. The first set of coronary segments ($n = 86$) during the calibration phase was used to construct an algorithm for the subsequent, prospective study ($n = 126$) during the validation phase. Histopathology was performed at 2-mm intervals according to a modified American Heart Association classification scheme. The authors defined a "lipid core plaque of interest" (LCP) as a fibroatheroma with a lipid core $>60^\circ$ in circumferential extent, $>200\text{-}\mu\text{m}$ thick, with a fibrous cap $<450\ \mu\text{m}$. In addition, a "lipid core burden index" (LCBI) was calculated based on the amount of lipid core in the entire scanned artery on a 0 to 1,000 scale. The analysis was double-blinded: those constructing the algorithm in the calibration phase did not have access to histologic data from the validation phase, and those performing NIRS and histologic analyses during the validation phase did not have access to the algorithm.

The results of the NIRS algorithm for each pullback generated a color map indicating the lipid content of the arterial wall viewed from the luminal surface termed a chemogram. The LCBI was based on the fraction of chemogram pixel intensity, while the block chemogram represents a summary of the presence of LCP at 2-mm intervals in 4 probability categories. The pre-specified end point of the study was the ability of NIRS to detect localized LCP in 2-mm blocks of the coronary artery segment evaluated using receiver-operator characteristic analysis of the NIR chemogram versus the LCP histology values. The LCPs were present in 4.3% blocks from the validation hearts with the algorithm prospectively identifying LCP with a receiver-operator characteristic area of 0.80 (95% confidence interval: 0.76 to 0.85). The LCBI detected the presence or absence of any fibroatheroma with an area under the curve of 0.86 (95% confidence interval: 0.81 to 0.91). Both of these values are consistent with the accuracy of current diagnostic modalities. Retrospective, exploratory analysis conducted in extreme artery segments with either no or extensive fibroatheroma yielded even higher area under the curve validation. While this latter type of exploratory analysis represents an artificial situation, it does support the ability of NIRS to discriminate tissue types based on chemical composition. The main limitation of the study as outlined by the authors is the ex vivo nature without the dynamic motion and tortuous anatomy of the coronary vasculature. The

authors conclude that NIRS accurately identifies LCP in coronary autopsy specimens and that this capability will assist in the management of patients with coronary artery disease (CAD).

This study builds on previous evidence that NIRS can identify plaque composition and features associated with plaque vulnerability in post-mortem human specimens (12,13). The authors should be commended for conducting a rigorous calibration and validation study of this novel intravascular imaging device for VP that has not been uniformly adopted by other current clinically available techniques. This autopsy validation, together with early clinical results, provides a new tool to identify lipid core plaques in patients with atherosclerosis. The authors discuss the potential use of NIRS for improved risk stratification in patients at higher risk of subsequent coronary events, as well as potentially guiding therapy—whether it be medical, catheter-based (stent), or even surgical. The combination of NIRS (biology) with current IVUS or optical coherence tomography imaging devices (anatomic) would certainly improve diagnostic information at the time of intravascular assessment. The ultimate goal, however, in assessing VP is to prevent ACS in patients at highest risk. Although noninvasive imaging holds future promise for risk stratification, the compelling near-term opportunity rests with CAD patients who present daily to the catheterization laboratory (16). Lesion-level risk stratification with these invasive VP imaging devices should be seen as complementary to current diagnostic techniques. Utilizing traditional and evolving markers of risk gives a more complete picture in assessing the patient's prognosis by defining the stage of atherosclerotic disease and aligning the appropriate treatment. Ongoing natural history studies and registries are needed to determine the preventative effectiveness of these diagnostic techniques as well as proposed interventional VP therapies. In conclusion, further studies are warranted to determine if detection of LCP by NIRS imaging will contribute to enhanced prediction of outcomes in patients with known CAD.

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